REMARKS/ARGUMENTS

Present Invention and Pending Claims

Claims 1-23 are pending. Claims 1-14 are directed to a pharmaceutical composition. Claims 15-23 are directed to a method of treating a cardiovascular disorder.

Summary of the Claim Amendments

Claims 2-4 have been amended to add the term "inhibitor" so as to recite a cholesteryl ester transfer protein inhibitor. Claim 2 has been amended to recite "more than 50%," as supported by the substitute specification at, for example, paragraph 0079. Claims 3 and 5 have been amended to recite "wherein the amount of inhibitor in amorphous form does not exceed about 10%," as supported by the substitute specification at, for example, paragraph 0079. The term "or prophylaxis" has been deleted from claim 15. Claim 10 has been labeled as withdrawn. No new matter has been added by way of these amendments.

Information Disclosure Statement

The Office Action indicates that references BZ-CK, CS-CU, DH, DO, and DR-EJ identified on the PTO-1449 form accompanying Applicants' Information Disclosure Statement dated October 8, 2004, were not considered because these references either were not provided or were not in English.

A copy of each of the indicated references was submitted by Applicants at the time Applicants filed the Information Disclosure Statement, and the USPTO acknowledged receipt of the references (see attached copy of USPTO stamped postcard receipt). The USPTO's PAIR system contains electronic copies of references BZ-CK, CS-CU, DH, and DO. As a convenience to the USPTO, Applicants re-submit herewith electronic copies of references DR-EJ, which – for reasons unknown to Applicants – are not present in the USPTO's PAIR system.

References DS-DU, DW-EA, ED, EE, and EH-EJ are in the English language. References DR and DV are not in English, but Applicants submitted these references along with English language translations thereof. References BZ-CK, CS-CU, DH, DO, EB, EC,

EF, and EG also are not in English, but Applicants submitted these references along with English language abstracts thereof.

In accordance with 37 C.F.R. § 1.98(a)(3), Applicants can submit a non-English language reference to the USPTO along with an English language equivalent/patent, an English language abstract, or an English language version of the search report or action by a foreign patent office in a counterpart foreign application indicating the degree of relevance found by the foreign patent office, whereupon the Examiner is required to consider the non-English reference. See also M.P.E.P. § 609.04(a)(III).

Accordingly, Applicants respectfully request that the Examiner consider the aforementioned references and confirm doing so by returning to Applicants the appropriately initialed PTO-1449 form.

Summary of the Office Action

The restriction requirement has been maintained.

Claims 2-4 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking antecedent basis.

Claims 2, 3, 5, 7-9, 11, 13, and 14 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 15-23 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Claims 5-9 and 11-13 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious over Gumkowski et al. (U.S. Patent Application Publication 2006/0014788) in view of Ault et al. (U.S. Patent 7,049,283).

Claims 5-9 and 11-13 have been rejected under 35 U.S.C. § 103(a), as allegedly obvious over Shinkai et al. I (U.S. Patent 6,426,365) in view of Sanbar et al. (*Circulation*, Volume XXXVIII, October 1968).

The Office rejects claims 1-9 and 11-23 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-24 of Shinkai et al. I (U.S. Patent 6,426,365) or Shinkai et al. II (U.S. Patent 6,753,346). The Office provisionally rejects claims 1-9 and 11-23 on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over (a) claims 1-18 of co-pending U.S. Patent Application 10/825,531, or (b) claims 1-5, 7-32, 34-52, and 54-83 of co-pending U.S. Patent Application 10/835,916.

Reconsideration of the pending claims is hereby requested.

Discussion of the Restriction Requirement

The Examiner has maintained the species election. Claims 1-9 and 11-23 read on the elected species. Claim 10 has been withdrawn from consideration by the Examiner, and Applicants have relabeled claim 10 accordingly.

Discussion of the Rejection Regarding Lack of Antecedent Basis

The term "cholesteryl ester transfer protein" reportedly lacks antecedent basis in claims 2-4. Claims 2-4 have been amended to add the term "inhibitor" to reflect the terminology recited in claim 1. In view of this amendment, this rejection of claims 2-4 has been overcome.

Discussion of the Indefiniteness Rejections

According to the Office Action, claim 2 is indefinite because of the term "a major portion." The term "a major portion" has been replaced with the equivalent term "more than 50%," in accordance with the disclosure in the specification at, for example, paragraph 0079.

The Examiner contends that the term "substantially" in claims 3, 5, 7-9, 11, 13, and 14 is indefinite. Claims 3 and 5 (and thus claims 7-9, 11, 13, and 14 dependent thereon) have been amended to further define the term "substantially" with the phrase "wherein the amount of inhibitor in amorphous form does not exceed about 10%," as defined by the specification at, for example, paragraph 0079.

In view of these amendments, the indefiniteness rejections have been rendered moot and should be withdrawn.

Discussion of the Enablement Rejection

The Office rejects claims 15-23 for allegedly lacking enablement for the prophylaxis of a cardiovascular disorder. In order to advance prosecution, claim 15 (and, thus, claims 16-23 dependent thereon) has been amended to no longer recite "prophylaxis." Applicants believe that the enablement rejection is moot in view of this amendment and request that the enablement rejection be withdrawn.

Discussion of the Obviousness Rejections

A. Gumkowski et al. and Ault et al.

Claims 5-9 and 11-13 allegedly are obvious over Gumkowski et al. in view of Ault et al. The Office contends that Gumkowski et al. teaches pharmaceutical compositions comprising a cholesteryl ester transfer protein (CETP) inhibitor and other co-solvents, surfactants, and optionally a digestible oil. Gumkowski et al. discloses the administration of the oral formulation in encapsulated dosage forms such as soft or hard gelatin capsules or aqueous oral emulsions formed by adding the oral formulation to water or another aqueous liquid. The encapsulated formulations reportedly provide enhanced bioavailability because of increased concentrations of CETP inhibitors. Gumkowski et al. further discloses the administration of the pharmaceutical compositions to raise high density lipoprotein (HDL), lower low density lipoprotein (LDL), and to treat atherosclerosis.

The Office appears to concede that Gumkowski et al. does not teach or suggest a composition comprising crospovidone. To compensate for this deficiency, the Office cites Ault et al. Ault et al. discloses a composition for oral delivery comprising an active agent, crospovidone or povidone, and a delivery agent for the active agent. Ault et al. reportedly describes that the composition comprising crospovidone versus compositions without crospovidone provided enhanced bioavailability of the active agent (col. 9, lines 34-38).

The Office has failed to present a *prima facie* case of obviousness. More specifically, the Office has failed to provide the bases of the basic factual inquiries related to obviousness

(i.e., "a *Graham* factor analysis"). While the Office has apparently set forth the scope and content of the prior art (the first factor), the Office Action does not recite the differences between the claimed invention and the prior art (the second factor). For example, it is not clearly acknowledged in the Office Action that Gumkowski et al. does not disclose the use of a water-insoluble concentration-enhancing additive, such as crospovidone. In addition, the Office Action does not acknowledge the utility of the formulations described by Ault et al., which are useful for the treatment of bone related diseases and calcium disorders (col. 2, lines 30-35). The Office also fails to make a proper *Graham* factor analysis because the level of ordinary skill in the pertinent art is not defined (the third factor).

After the *Graham* factual inquires have been set forth, the Office must provide evidence of *why* the differences between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. Further indication that the Office has failed to present a *prima facie* case of obviousness is that the Office has not pointed to anything in either cited reference to indicate *why* one would combine the two disclosures. Applicants maintain that nothing in either of Gumkowski et al. or Ault et al. would lead one of ordinary skill in the art to arrive at the *specific* composition or method of the pending claims that require (a) a pharmaceutical composition comprising (i) a substantially crystalline CETP inhibitor of Formula I and (ii) a water-insoluble concentration-enhancing additive (e.g., claims 5-9 and 11-14), or (b) a method for the treatment of a cardiovascular disorder by administration of the inventive composition (e.g., claims 15-23).

Gumkowski et al. is directed to oral formulations that increase the solubility of CETP inhibitors, which in turn improves the bioavailability thereof (see paragraph 0013). These compositions do not contain a water-insoluble concentration-enhancing additive, such as crospovidone. The Office has failed to point out why one of ordinary skill in the art would seek out an additional reference for some teaching to supplement the composition disclosed by Gumkowski et al.

Even if, for some unspecified reason, one of ordinary skill in the art sought another reference, that artisan would not be led to the disclosure of Ault et al. Ault et al. is not directed to the use of CETP inhibitors at all or the treatment of cardiovascular disorders. Without prior knowledge of the subject matter of the pending claims, one would not turn to

the disclosure of the unrelated subject matter of Ault et al. when other references likely are available that remedy the known low solubility and low oral bioavailability of CETP inhibitors (see, e.g., paragraph 0002 of Gumkowski et al.).

Moreover, without any teaching of, or pointer to, a compound of Formula I (e.g., *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate, "JTT-705") in Gumkowski et al., one of ordinary skill in the art could be easily led to a disclosure reciting any number of CETP inhibitors other than JTT-705. Gumkowski et al. specifically recites that the "invention is not limited by any particular structure or group of CETP inhibitors" (paragraph 0110). Further, while Gumkowski et al. discloses that the blood levels of *some* CETP inhibitors, when administered with triglyceride solutions, are increased (see paragraph 0012), Gumkowski et al. does not disclose whether the blood level of the compound of Formula I recited in the pending claims in combination with triglyceride solutions would be increased. One claimed compound of Formula I is disclosed only in an extensive list of hundreds of CETP inhibitors that can be used in the oral formulation of Gumkowski et al. (see paragraphs 0113-1035). The Examiner has failed to describe why one would knowingly select a compound of Formula I (e.g., JTT-705) from Gumkowski et al. and not one of the other inhibitors recited therein, i.e., paragraphs 0113-1035, and combine it with a water-insoluble concentration-enhancing additive (e.g., crospovidone) – without prior knowledge of the present invention.

Since a *prima facie* case of obviousness has not been established, Applicants submit that the obviousness rejection based on Gumkowski et al. and Ault et al. is without merit and should be withdrawn.

B. Shinkai et al. and Sanbar et al.

Claims 5-9 and 11-13 allegedly are obvious over Shinkai et al. I in view of Sanbar et al. Shinkai et al. discloses compositions comprising a CETP inhibitor, including JTT-705 (Example 26), and known carriers, sweeteners, and flavor improving agents. The compositions are useful for treating atherosclerosis or hyperlipidemia because the CETP inhibitor increases HDL and lowers LDL (col. 4, lines 21-27).

The Office appears to concede that Shinkai et al. I does not teach or suggest a composition comprising crospovidone. To compensate for this deficiency, the Office relies on Sanbar et al. Sanbar et al. allegedly discloses intravenous administration of polyvinylpyrrolidone (PVP) to patients with hyperlipidemia. The PVP reportedly had a hypolipidemic effect by lowering serum cholesterol and triglyceride concentrations (page 774, "Discussion"). The Office asserts that polyvinylpolypyrrolidone is another commonly used name for crospovidone.

According to the Office, it would have been obvious to combine the disclosures of Shinkai et al. I and Sanbar et al. to arrive at the present invention because both are directed to hyperlipidemia.

Pending claims 5-9 and 11-23 require, *inter alia*, a *water-insoluble* concentration-enhancing additive, such as crospovidone. The Office relies on the disclosure of Sanbar et al. for a disclosure of crospovidone, yet Sanbar et al. discloses *povidone* which is *water-soluble* (not crospovidone, which is water-insoluble).

Povidone is **p**oly**v**inyl**p**yrrolidone or PVP, whereas crospovidone is **p**oly**v**inyl**p**oly**p**yrrolidone or PVPP. Crospovidone is cross-linked PVP, and, unlike PVP, crospovidone is water-insoluble. See, e.g., pages 184-185 and 508-513 from Rowe et al. Handbook of Pharmaceutical Excipients, 4th Edition. London: Pharmaceutical Press, 2003 (submitted herewith). Since PVP is not the same as crospovidone, Sanbar et al. does not teach or suggest a composition comprising a water-insoluble concentration-enhancing additive, as required by the pending claims.

The Examiner specifically addresses claims 6, 7, 13, and 18-23. Since these claims are directly or indirectly dependent on independent claim 1 or 5, these claims also require a water-insoluble concentration-enhancing additive, such as crospovidone, and the foregoing discussion applies equally to claims 6, 7, 13, and 18-23 (as well as claims 8, 11, 12, and 14-17).

Since the cited references do not teach or suggest all the elements of the composition or method of claims 5-9 and 11-23, it cannot be said that these claims are obvious in view of

Shinkai et al. I and Sanbar et al. Accordingly, this obviousness rejection should be withdrawn.

Discussion of the Obviousness-type Double Patenting Rejections

The Office has rejected claims 1-9 and 11-23 for obviousness-type double patenting in view of several references. These rejections are traversed for the following reasons.

A. Shinkai et al. I, Shinkai et al. II, or Shinkai et al. III

Shinkai et al. I contains claims directed to a compound that encompasses the species of the compound recited in the pending claims. Shinkai et al. I contains only compound claims.

Shinkai et al. II contains claims directed to *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate and a composition thereof, as well as a method of inhibiting CETP activity, a method of increasing HDL, a method of decreasing LDL, a method of treating or preventing atherosclerosis, and a method of treating or preventing hyperlipidemia.

U.S. Patent Application 10/825,531 issued as U.S. Patent 7,271,196 ("Shinkai et al. III"). Shinkai et al. III contains compound claims, composition claims, and process claims (specifically, a method of preparing a compound).

With respect to an obviousness-type double patenting rejection, such a rejection is only proper when the pending claims of an application recite an obvious variation of the invention that is *claimed* in a patent or patent application (MPEP § 804.II.B.1). The *specifications* of the cited patents (i.e., Shinkai et al. I, II, and III) are not involved in such an analysis. In the instant case, the *claims* of the cited patents do not teach or suggest (a) a pharmaceutical composition comprising a CETP inhibitor and crospovidone (e.g., claim 1), (b) a pharmaceutical composition comprising (i) a substantially crystalline CETP inhibitor of Formula I, in which the amount of inhibitor in amorphous form does not exceed about 10% and (ii) a water-insoluble concentration-enhancing additive (e.g., claim 5), or (c) a method for the treatment of a cardiovascular disorder by administration of a pharmaceutical composition comprising a CETP inhibitor and crospovidone (e.g., claim 15), as recited in the pending

claims. More specifically, the *claims* of Shinkai et al. I, II,.and III do not teach or suggest a pharmaceutical composition comprising a water-insoluble concentration-enhancing additive, such as crospovidone, or a method of use thereof.

Accordingly, the subject matter of the pending claims cannot be considered obvious in view of the claims of the cited patents, and the obviousness-type double patenting rejections should be withdrawn.

B. U.S. Patent Application 10/835,916

The '916 application recites claims directed to a combination of two active ingredients comprising (a) *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate or a prodrug thereof, and (b) at least one HMG CoA reductase inhibitor (e.g., a statin), as well as a method of treating a cardiovascular disorder by administering a combination of (a) *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate or a prodrug thereof, and (b) at least one HMG CoA reductase inhibitor (e.g., a statin). The claims of the '916 application do not teach or suggest (a) a pharmaceutical composition comprising a CETP inhibitor and crospovidone (e.g., claim 1), (b) a pharmaceutical composition comprising (i) a substantially crystalline CETP inhibitor of Formula I, in which the amount of inhibitor in amorphous form does not exceed about 10% and (ii) a water-insoluble concentration-enhancing additive (e.g., claim 5), or (c) a method for the treatment of a cardiovascular disorder by administration of a pharmaceutical composition comprising a CETP inhibitor and crospovidone (e.g., claim 15), as recited in the pending claims.

Moreover, the obviousness-type double patenting rejection with respect to the '916 application is provisional because the '916 application has not yet issued as a patent. As stated in M.P.E.P. § 1504.06, "[i]f a provisional double patenting rejection (of any type) is the only rejection remaining in two conflicting applications, the examiner should withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent."

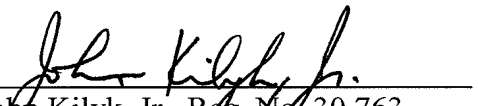
The present application has a filing date of March 17, 2004, whereas the '916 application has a filing date of April 30, 2004. Thus, irrespective of the merits of the

obviousness-type double patenting rejection, the present application should be passed to issuance without the need to address the obviousness-type double patenting rejection over the '916 application. If appropriate, an obviousness-type double patenting rejection may be raised in the prosecution of the '916 application. In such an event, Applicants will address the obviousness-type double patenting rejection at that time in connection with the prosecution of the '916 application.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,



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